REMARKS/ARGUMENTS

Claims 1, 2, 4, 5, and 7-12 are now pending in the application. In order to expedite the examination of this application, Claims 42 and 43 are canceled herein without prejudice toward the filing of the same or similar claims in a continuing application.

Although it was not requested by the Examiner in this action, Applicants note in the PAIR system that an error was found in the submitted Sequence Listing with regard to the total number of sequences. Accordingly, a corrected Substitute Sequence Listing is enclosed herewith.

Claim Rejections –35 U.S.C. 112

Item 4:

Claims 42 and 43 were rejected under 35 U.S.C. 112, first paragraph, as allegedly failing to comply with the written description requirement. As Claims 42 and 43 have been canceled, the rejection is moot. Accordingly, withdrawal of this rejection is respectfully requested.

Item 5:

Claims 42 and 43 were rejected under 35 U.S.C. 112, second paragraph, as allegedly being indefinite. As Claims 42 and 43 have been canceled, the rejection is moot. Accordingly, withdrawal of this rejection is respectfully requested.

Claim Rejections - 35 U.S.C 102(b)

Item 6:

Claims 42 and 43 were rejected under 35 U.S.C. 102(b) as being allegedly anticipated by Arnold et al. as evidenced by Pochart. As Claims 42 and 43 have been canceled, the rejection is moot. Accordingly, withdrawal of this rejection is respectfully requested.

Claim Rejections - 35 U.S.C 103(a)

Items 7-8:

Claims 1-2, 4, and 7-12 were rejected under 35 U.S.C. 103(a) over Arnold et al. in view of Mashal. Arnold et al. teach a method for evolving a polynucleotide toward acquisition of a desired property by exposing a heteroduplex to a cellular DNA repair system to convert the heteroduplexes to parental polynucleotides or recombined polynucleotide variants. Mashal et al. teach the detection of mutations by cleavage of DNA heteroduplexes with bacteriophage resolvases such as T4 endonuclease VII. The Examiner suggests that it would be obvious to combine the T4 endonuclease VII of Mashal with the cellular DNA repair system of Arnold et al. This rejection is respectfully traversed. One of ordinary skill in the art at the time of the invention would have expected that such a combination might result in an inoperative invention, or at best reduced efficiency.

According to Lahue et al. PNAS 84(1987)1482-1486 (cited in an earlier IDS), the *E. coli* DNA repair system includes a protein that recognizes mismatches but does not cleave (mut S), another protein that cleaves the DNA at a hemimethylated dGATC site, but does not recognize mismatches, and a protein to bridge these two. Other proteins in the *E. coli* repair system described by Lahue et al. include DNA helicase II and single-stranded DNA binding protein (SSB), Exonuclease I for removing large tracts of DNA that may include the mismatch site, and the DNA Pol III holoenzyme for resynthesizing the large tracts of DNA.

It wouldn't be obvious to take a mismatch-directed strand-cleaving enzyme of the sort exemplified in the currently claimed method and add it to a system that uses a DNA repair system. It isn't at all clear what benefit, if any, would result if such an enzyme were added to a cell extract containing a cellular DNA repair system. Since the DNA repair systems have evolved to already be fully functional in repairing DNA and the enzymes act in a highly coordinated manner, and since the enzymes with mismatch directed strand cleavage activity used in the currently claimed method of making sequence variants are not thought to be involved in cellular DNA repair systems, there would not be any motivation to add such an enzyme into a DNA repair system. Indeed, in contemplating the mechanism of such cellular DNA repair systems, one of ordinary skill in the art might expect that addition of a mismatch endonuclease of the type used in the presently claimed method to a DNA repair system would cause nicking of the heteroduplex at sites of mismatch such that when the DNA repair system started stripping away a strand of the duplex it might well start crossing places where the opposite strand had been nicked by the mismatch endonuclease, resulting in double-strand breaks of the DNA and destruction of the molecule. Hence, one of ordinary skill in the art might expect the "mismatch-directed strand cleavage activity" of the current method to be fundamentally incompatible with a cellular DNA repair system of the sort exemplified by Arnold et al., resulting in an inoperative invention or at least a reduction in recovered products. As the cited references, alone or in combination, do not teach or suggest the claimed method, reconsideration and withdrawal of the rejection is respectfully requested.

Item 9.

Claim 5 was rejected under 35 U.S.C. 103(a) over Arnold et al. in view of Mashal and in further view of Wetmur. This rejection is respectfully traversed.

The failure of Arnold et al. and Mashal et al. to teach or suggest the currently claimed method is discussed above. Wetmur teachs a system utilizing MutS homologs to bind bulge loops in heteroduplex nucleic acids. Wetmur references a method called genome mismatch scanning, a method for whole genome scanning which utilizes *E. coli* MutS and the other enzymes of the mismatch repair system. Wetmur does not compensate for the deficiencies of Arnold et al. and Mashal et al. noted above. Application of the method of Arnold et al. in view of Mashal et al. to a whole genome does not result in the currently claimed method. As the cited references, alone or in combination, do not teach or suggest the claimed method, reconsideration and withdrawal of the rejection is respectfully requested.

Item 10:

Applicants acknowledge the withdrawal of some rejections.

The Examiner states that the color drawings accompanying the Padgett Declaration were not received by the office. However, Applicants received a return postcard from the USTPO stamped with a receipt date of August 15, 2007 acknowledging receipt of the figures. If the Examiner is unable to locate the figures, Applicants would be pleased to provide another copy upon request.

Claims 1, 2, 4, 5, and 7-12 are now pending in the application. In view of the current claim amendments and comments above, the rejections have been overcome. Reconsideration, withdrawal of the rejections and early indication of allowance are respectfully requested. If any issues remain, the examiner is encouraged to call the undersigned for prompt resolution.

If needed, Applicants petition for an extension of time under the provisions of 37 CFR 1.136(a) for sufficient time to accept this response. The commissioner hereby is authorized to charge payment of any fees under 37 CFR § 1.17, which may become due in connection with the instant application or credit any overpayment to Deposit Account No.504391.

Respectfully submitted,

Date: March 3, 2008

/Wayne Fitzmaurice/
Wayne P. Fitzmaurice
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Enclosures: Petition for a One-Month Extension of Time (1 page)
Substitute Sequence Listing

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